CHANGES IN CEREBRAL BLOOD FLOW VELOCITIES MEASURED BY DOPPLER ULTRASONOGRAPHY AFTER HYPOXIC-ISCHEMIC INJURY IN NEWBORNS

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Abstract: *Perinatal hypoxic-ischemic insults may lead to significant morbidity and mortality in neonates and infants. Because anoxic-ischemic process is related to changes in cerebral blood flow, a hemodynamic study is required, and can guide towards early diagnosis and prognosis. The aim was to investigate cerebral hemodynamics with Doppler-ultrasonography and search for correlations between cerebral hemodynamic parameters and other changes in asphyxia. Material and methods: 21 asphyxiated newborns, admitted to our intensive care unit and 200 healthy ones were studied in the first 72 hours of life. Results: cerebral blood velocities were initially significantly lower in asphyxiated infants than in control group, after 12 hours diastolic velocity increased and resistive index decreased, and these findings remained constant after 48 hours in babies with poor outcome. Conclusions: Doppler-ultrasonography is a reliable tool in clinician's hands in detecting the impairment of autoregulation due to hypoxic-ischemic injury in newborns and evaluating prognosis.*

Cuvinte cheie: *injurie hipoxic-ischemică perinatală, ultrasonografie Doppler transfontanelară, flux sanguin cerebral*

Rezumat: *Injuria hipoxic-ischemică perinatală poate determina creşterea semnificativă a morbidităţii şi mortalităţii neonatale şi infantile. Procesul anoxic-ischemic este strâns legat de modificările fluxului sanguin cerebral, de aceea un studiu hemodinamic ar fi util în diagnosticul precoce şi enunţarea prognosticului. Scopul lucrării este de a investiga hemodinamica cerebrală prin intermediul ecografiei Doppler şi căutarea corelaţiilor dintre parametrii hemodinamici cerebrali şi alte modificări în asfixie. Material şi metode: am studiat parametrii menţionaţi la 21 nou-născuţi cu asfixie la naştere şi 200 nou-născuţi sănătoşi în primele 72 ore de viaţă. Rezultate: velocităţile cerebrale iniţial au fost subnormale la nou-născuţii cu asfixie, a urmat creşterea componentei diastolice după 12 ore şi scăderea indicelui de rezistivitate, modificări persistente după 48 ore la copiii cu evoluţie nefavorabilă. Concluzii: ultrasonografia Doppler este o metodă de încredere în mâinile clinicianului, utilă pentru evaluarea afectării autoreglării cerebrale secundare injuriei hipoxic-ischemice şi pentru estimarea unui prognostic pe termen lung.*

INTRODUCTION

Perinatal asphyxia is the most common cause of neurologic injury in the neonate and may lead to significant morbidity and mortality. The condition occurs in 1% to 1,5% live births and is inversely related to gestational age (GA) and birth weight, causing 20% of perinatal deaths.(1) Clinical studies showed that hemodynamic and blood gas abnormalities that can occur ante- or intrapartum could lead to central nervous system damage resulting in different degrees of neuropsychomotor sequelae.(2)

The morphological approach to anoxic-ischemic lesions is known to be difficult using simple gray-scale ultrasonography, due to the lack of specificity of the method in the first hours, and the later cortical lesions are not accesable to sonographic examination.(3) Because anoxic-ischemic process is closely related to changes of the cerebral blood flow (CBF), a hemodynamic study is required, an active investigation that can guide towards early diagnosis and prognosis. Doppler ultrasonography is a non-invasive method, allowing repeated and safe assessment of neonatal cerebral hemodynamics and showing consistent changes of CBF velocities in infants with perinatal asphyxia.(4,5) The exam can be done at the bedside, without sedation, has a relatively low-cost, and does not influence the status or the treatment of the infant.(3,6)

THE AIM OF THE STUDY

The aim of the study was to investigate cerebral hemodynamics after perinatal hypoxic-ischemic injury and to find correlations between the supposed changes and modifications of other hemodynamic, metabolic, hematologic and homeostatic parameters and, also to evaluate the later outcome relation to these findings.

MATERIAL AND METHOD

The study was a prospective one between 1th Jan 2006 and 31st July 2009, developed in Mures County Emergency Hospital, Neonatology and Obstetrics and Gynecology Departments.

We studied two groups: 1. 21 term newborns, all meeting the clinical and lab criteria for perinatal asphyxia, in conformity with WHO, AAP, and ACOG definition. Newborns with birth trauma, medications before birth, and fetal or maternal illness that could had led to difficulties adaptation to the extrauterine conditions, were excluded. 2. The controll group consisted of 200 healthy neonates, with normal postanatal adaptation.

Infants included in the study were examined at birth, Apgar scores, and GA (based on Ballard score) were assigned.

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Complete physical exams were done at birth and dayly or whenever needed, noting the degree of neurological syndrome according to the Sarnat & Sarnat staging, also the evolution of the case. Newborns with asphyxia were cared for in our neonatal intensive care unit, maintaining an adequate ventilation and oxygenation, corection and maintanence of the acidobase and hydro-electrolytic balance, sustaining the cardiac output and blood pressure. Temperature control was ensured, and also the treatment of seizures when necessary. The control group was cared for in rooming-in system, infants receiving routine care, breastfed and discharged on the fourth day after birth.

For both groups, the arterial pH, pCO_2 (mmHg), pO_2 (mmHg), mean arterial blood pressure (MBP in mmHg) in the first 12 hours, at 24, 48, and after 72 hours of life were measured.

The velocities of the CBF were measured using colour duplex Doppler scanner Philips, En-Visor B.0.1. software, using 5-12 MHz frequency sectorial transducers. The recordings of the CBF velocities were made in supination, quiet state, and with no gross body movements through the anterior fontanel. Anterior cerebral artery (ACA) was visualized in the sagittal plane and the signals were recorded from the point midway between the most inferior border of the corpus callosum and the vessel origin from the circle of Willis. The angle correction was performed if the angle was higher than 30˚ (exceptional due to the anatomy of this artery). The resistive index (RI) was calculated according to the formula RI = (VS-VD)/VS) where VS – systolic velocity, VD – diastolic velocity.

ANOVA and Newman-Keuls tests were used for the statistical analysis, to compare data at different moments in asphyxiated and healthy infants, p values of < 0.05 were considered statistically significant at a confidence interval of 95%. We obtained informed consent from at least one of the newborn's parents, and respected the confidentiality of the data.

RESULTS

The newborns with asphyxia were divided in 9 cases (42.85%) with stage III, 8 cases (38.09%) with stage II and 4 cases (19.05%) with stage I hypoxic-ischemic encephalopathia (HIE) after Sarnat & Sarnat staging. In asphyxiated neonates the GA was 38,2 ± 1,6 weeks, and the GA of the healthy neonates was 38.9 ± 1.4 weeks. Birth weight of the healthy newborns was 3271.6 ± 320.9g, while in asphyxiated babies it was 3416.7 ± 586.3g, without statistical difference between the groups ($p > 0.05$).

PO_2, pCO_2, MBP, systolic and end-diastolic peak flow velocities and RI values in ACA in the first 72 hours of life were compared between the two groups. We found statistical difference between the groups in all the moments of the examination for the mean of the main parameters of hemodynamic and blood gas adaptation, as shown in Table I., although the patients with HIE Sarnat I reached normal values after 48 hours of life. There were statistically significant differences ($p < 0.05$) between the groups between the ACA both systolic and end-diastolic flow velocity in the first days, systolic velocity rising from an inferior value to very high values in this period, and end-diastolic velocities having lower values in the first 12 hours, and increasing dramatically in the next 24 hours. Sarnat I staged asphyxiated babies presented normalized systolic and diastolic velocities in the first 48 hours, while Sarnat II staged infants had greater changes of the diastolic velocities, without normalization even after 72 hours. Statistical mean, minimum, maximum, median and standard deviation for each variable are listed on Table II. Resistive index values were lower in the measured vessel in the asphyxiated infants compared with controls after 12 hours (Figure 1). We determined that RI values of anterior cerebral artery were 0.62-0.80 in healthy infants and 0.35-0.98 in asphyxiated infants in the first 3 days of life. Changes from very high to very low values were found in severe asphyxic patients.

In asphyxiated newborns, a significant direct correlation was found between pCO_2 and systolic and diastolic velocities after 24 hours (r: 0.6838-0.9617, $p << 0.05$), and an inverse correlation between the velocities and pO_2 (r: -0.6991- -0.9784, $p < 0.05$). There was a constant strong correlation between systolic velocity and blood pressure.

We also found significant correlation between the severity of HIE and the values of end-diastolic velocity after 48 hours confirmed by the correlation coefficient $r > 0,5$ and $p < 0,05$ respectively negative correlation with RI values ($r > -0,5$; $p < 0,05$). RI values increased significantly in neonates with normal outcome, decreased initially and maintaned this low level in cases with later neurological sequelae, and showed continuous decrease in severe HIE ended with exitus.

Table no. 1. Statistical indicators in asphyxic and control groups regarding pCO_2, PO_2 and MBP

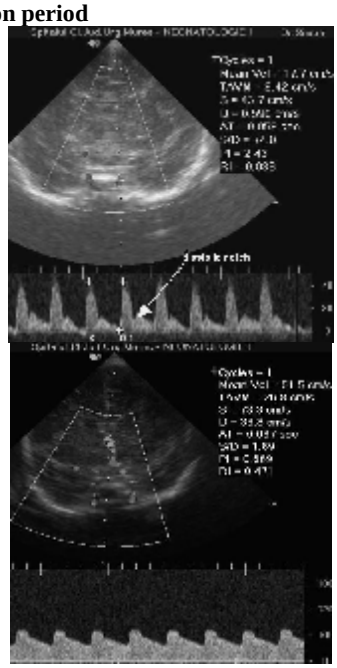
Moment/ group	Measured variables					
	PCO_2		PO_2		MBP	
	Mean ± SD	Median (min-Max)	Mean ± SD	Median (min-Max)	Mean ± SD	Median (min-Max)
at birth control	39.7±5.0	39.0 (27.3-55.0)	28.0±6.9	29.6 (16.1-40.1)	51.4±7.9	50 (37-67)
at birth asphyxia	77.5±12.4	78.9 (52.3-92.3)	16.1±1.4	16.5 (13.6-18.3)	36.47±3.9	36 (27-43)
24h control	39.1±3.3	37.7 (35.0-49.8)	79.3±5.0	79.3 (73.0-92.0)	57.8±6.9	58 (39-75)
24h asphyxia	62±15.6	56.7 (45.6-98.8)	47±8.8	46.3 (32.3-67.8)	46.62±11.79	42 (34-72)
48h control	38.7±3.1	37.9 (35.0-47.6)	81.3±7.2	79.3 (69.8-100.6)	57.1±7.7	58 (41-75)
48h asphyxia	63.5±30.9	52.5 (35.5-160.2)	55.5±12.7	56.9 (32.5-73.5)	51.85±12.5	52 (34-77)
72h control	39.2±2.6	38.8 (35.1-44.8)	81.9±7.0	80.0 (71.5-102.9)	62.5±8.3	63 (41-80)
72h asphyxia	57.6±30.5	47.5 (36-166.8)	60.3±15.5	63.3 (34-89.4)	53.55±11.2	54 (34-82)

Table no. 2. Cerebral hemodynamic parameters in studied groups in the first 72 h of life

Moment/ group	Measured variables					
	PSV		EDV		RI	
	Mean ± SD	Median (min-Max)	Mean ± SD	Median (min-Max)	Mean ± SD	Median (min-Max)
<12h control	35.0±4.4	34.8 (24.4-45.2)	10.5±.1.9	10.9 (5.8-15.0)	0.70±0.03	0.69 (0.65-0.76)
<12h asphyxia	29.41±7.36	27.8 (14.2-45.9)	8.71±5.57	8.26 (0.47-21.4)	0.71±0.15	0.70 (0.5-0.98)
24h control	42.9±7.9	42.6 (30.2-59.6)	15.4±2.7	15.9 (11.3-23.8)	0.68±0.04	0.67 (0.62-0.8)
24h asphyxia	43.17±14.25	41.00 (16.8-77.2)	17.72±8.22	16.50 (5.78-35.50)	0.60±0.1	0.60 (0.35-0.8)
48h control	44.9±8.8	45.2 (30.1-60.2)	15.5±2.8	15.5 (11.8-23.8)	0.67±0.06	0.68 (0.6-0.75)
48h asphyxia	46.7±11.12	45.6 (28.3-70.6)	19.17±8.43	17.70 (6.37-40.10)	0.60±0.1	0.60 (0.43-0.77)
72h control	52.2±5.8	52.0 (36.3-64.9)	16.0±2.6	15.5 (10.0-20.7)	0.69±0.04	0.70 (0.63-0.76)
72h asphyxia	46.69±13.53	46.30 (21.6-93.6)	17.43±6.68	15.70 (8.85-38.10)	0.63±0.08	0.61 (0.49-0.76)

Seven newborns (33.33%) had a good outcome, 10 (47.62%) survived with different grades of neuropshychomotor sequelae, and 4 (19.04%) died during the first week of life. Morphological changes of the brain were cerebral atrophia, multicystic encephalomalacia and cisterna magna dilatation.

Figure no. 1. High RI values in the first day of life, with typical diastolic notch on the spectral curve, followed by low RI characteristic for luxurious perfusion, after 24 hours in the reperfusion period



DISCUSSION

During perinatal asphyxia, Doppler assessment of the CBF velocities reveals an early and prolonged drop of the RI due to increased end-diastolic in parallel with decreased absolute values of the velocities, a phenomenon observed at the level of several cerebral arteries. These abnormalities are reflecting the arterial vasodilatation due to complex mechanisms.(2,3) Fetal and maternal distress quickly leads to hypoxemia, hypercapnia and acidosis, causing cerebral vasodilatation, a protective response described by many authors during the intrauterine period.(7,8,9,10) In parallel with these changes, bradycardia and hypotension complete the clinical picture. Resuscitation at birth improves and normalizes the biological and hemodynamic parameters, reducing the disturbances that alter cerebral autoregulation. When arterial blood pressure returns to normal, normocapnia with normoxemia are restored, cerebral hemodynamic assessment of the newborn is important to evaluate the postasphyxic cerebral responses. Many authors believe that the luxurious perfusion denotes irreversible ischemic injury.(2,3,7) In the literature several pathophysiological hypothesis were developed. According to Volpe (2008), postischemic hyperemia is difficult to explain but could be caused by the combined effect of stored vasodilator agents and vascular wall damage.(11) In the opinion of others, postischemic brain swelling causes an increased tissular pressure, resulting in a protective increase of the diastolic flow.(9,12) When this compensatory mechanism is overloaded, reduction or even negative diastolic flow can occur, with poor prognosis. Couture (2001) thinks that detection of increased vascular resistance is important because of its correlation with a bad prognosis.(3)

Doppler investigation plays an important role in the accurate prognostic evaluation of anoxic-ischemic neonatal injury, especially because the sonographic morphological changes need 24-48 hours to be “seen”. A number of studies have shown high RI values with low velocities immediately after hypoxic insult, followed by increasing diastolic velocity and decreased RI in the next 12-24 hours (6,12,13-16), which can persist for several days, worsening the prognosis.

Our personal experience is based on the examination of 21 neonates with confirmed perinatal asphyxia. In these infants we observed systolic and diastolic velocities below normal in the first 12 hours of life, unstable arterial blood pressure and blood gases, although prompt resuscitation restored cardiac function shortly after birth. These changes could be explained by loss of cerebral autoregulation during intrauterine hypoxic-ischemic insult. Our data confirms the direct correlation between high initial RI values and the severity of HIE, and later the correlation between persistent low RI values and poor outcome. Systolic and diastolic velocities, and RI changed

differently in according to the severity of HIE, the lower and the longer the RI the worse the prognosis. In severe HIE cases diastolic velocities did not decreased significantly after 48 hours. We found a strong inverse correlation between diastolic velocities and pH values, a body's compensatory mechanism in acidosis. The loss of the autoregulation was demonstrated by the pressure passive character of the CBF, according to the data in the literature. The severity of later sequelae was directly correlated to the brain tissue destructions, a disadvantage in this respect being the maturity of the newborns, in conformity with literature studies.

CONCLUSIONS

Cerebral artery Doppler ultrasonography is a useful tool for the evaluation of the cerebral hemodynamics in asphyxiated newborns admitted to the neonatal intensive care unit. The degree and duration of cerebral hemodynamic alterations are in direct correlation with the severity of the disease and later outcome. RI and cerebral velocities are predictive for prognosis. Early Doppler investigation may be important in neonatal screening after hypoxic-ischemic injury to delineate the risk group, and, interpreted in respect to clinical data, it may lead the clinicians' management.

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